March 25, 1997 as U.S. patent number 5,614,191. - -

In The Claims

Please cancel claims 7-13 without prejudice; add new claims 14-22 as shown in Appendix A (attached hereto); and amend claims 1, 2, and 4-6 as shown in Appendix A. A clean set of the presently pending claims is shown in Appendix B (attached hereto).

REMARKS

Applicants have shown that human gliomas express a human IL13 (hIL13)-specific receptor that does not bind human IL4 (hIL4), and that intratumoral injection of cytotoxin-coupled hIL13 into animals bearing actively growing gliomas caused a significant reduction in the growth rate of the tumors. In some cases, this treatment eliminated any detectable tumors in such animals.

Application Status

A continued prosecution application (CPA) was filed on April 13, 2001. In the CPA, applicants requested and paid the fee for a three month suspension of action pursuant to 37 CFR 1.103(b). In response to the CPA filing, applicants received an office action mailed May 8, 2001. On May 11, 2001, the undersigned telephoned the Examiner to point out that the May 8, 2001 office action was apparently mailed by mistake, as the three month period of suspended action had not expired. The Examiner indicated that this office action was sent in error, and that applicants should request its withdrawal in their next written communication. Accordingly, withdrawal of the office action mailed May 8, 2001 is requested.

Prior to the filing of the CPA, a final Office Action mailed November 13, 2001 was outstanding (the "Office Action"). At that time, claims 1, 2 and 4-13 were pending in the subject application, claim 3 having been canceled by amendment and claims 7-13 having been withdrawn from consideration. Therefore, claims 1-2 and 4-6 were under consideration in the application. The Office Action rejected these claims for double patenting, under 35 USC 102, and/or under 35 USC 103.

In this amendment, claims 7-13 have been cancelled; claims 1, 2, and 4-6 have been revised; and new claims 14-22 have been added. Accordingly, claims 1, 2, 4-6, and 14-22 are now pending in the application. Consideration of these claims is respectfully requested.

This supplemental preliminary amendment is being submitted subsequent to a August 2, 2001 telephone conversation between the undersigned and Examiner Susan Ungar. The Examiner indicated that newly added claims 14-22 must appear in Appendix A and requested that this amendment be faxed to (703)746-3142. Accordingly, Appendix A has been so modified. Entry and consideration of this amendment is respectfully requested.

Obviousness-Type Double Patenting

Although applicants respectfully disagree with the prior double patenting rejection, the amendments made herein further distinguish the presently pending claims from the claims of the '191 patent. In particular, amended claim 1 now recites:

> 1. A method of reducing the rate of growth of glioma cells in vivo in a mammalian subject, the glioma cells comprising an IL13-specific receptor, comprising the step of: delivering into the subject a molecule having an IL13-moiety and a cytotoxic moiety in an amount effective to reduce the rate of growth of the glioma cells.

Thus claim 1 includes at least one limitation not described or suggested by the '191 patent, namely that the method relates in particular to glioma cells (note that claim 2 was not rejected for double patenting in the Office Action). In comparison, the only experiments described in the '191 patent were those for tumor cells other than gliomas (i.e., renal cell, stomach, skin, and colon carcinoma cell lines, and various other cell lines derived from the hematopoietic system). And as pointed out in the specification at page 7, lines 2-12, previous studies showed (1) that glioma cells that express an antigen in situ lose expression of that antigen when explanted and cultured in vitro; and (2) that overexpression of a molecule observed in in vitro cell cultures did not occur in the in situ situation. Therefore, since the '191 patent is silent with regard to glioma cells, and since cellular antigen expression is known to vary in glioma cells depending on whether the cells are in in vitro cell cultures or located in situ in a mammalian subject, it does not teach or suggest the method of amended claim 1. Accordingly, applicants submit that neither claim 1 nor any claim depending from claim 1 is properly subject to an obviousness-type double patenting rejection in view of the '191 patent.

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As indicated above, the '191 patent does not mention a glioma cell or suggest the method of amended claim 1 or new independent claim 18. Thus, applicants submit that the inventions of amended claim 1, new independent claim 18, and all claims depending from them are both novel and unobvious over the '191 patent.

Debinski et al. (Abstract, The Society of Neuro-Oncology, 1998; the "Debinski Abstract")

Accompanying this amendment are the declarations of the present inventors declaring that they were the only inventors of the subject matter described in the Debinski Abstract.

Debinski et al. (J. Biol. Chem., 1996, 271:22428; the "Debinski Paper")

The Debinski Paper discloses that established glioma cell lines and primary cultures of glioblastoma multiforme cells are sensitive to hIL13-based toxins in in vitro assays. None of the experiments of the Debinski Paper were performed in situ. As indicated above, there are significant differences between in vitro assays and the in situ situation. Accordingly, the Debinski Paper does not provide the requisite teaching to render the presently pending claims unpatentable.

Conclusion

The currently pending claims are supported throughout the specification and are patentable over the prior art. No new matter has been added. This application is now in full condition for allowance, and such action is respectfully requested.

No fee is believed due for this amendment or accompanying declarations. The Commissioner is, however, hereby authorized to charge any underpayment of fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 50-0951.

Applicants invite the Examiner to call the undersigned if clarification is needed on any matter within this Amendment, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Date: August 2, 2001

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APPENDIX A

1. (Amended) A method of reducing the rate of growth of glioma [tumor] cells in vivo in a mammalian subject, the glioma [tumor] cells comprising an IL13-specific receptor that specifically binds IL13 but not IL4, comprising the step of: delivering into the subject a molecule having an IL13-moiety and a cytotoxic moiety in an amount effective to reduce the rate of growth of the glioma [tumor] cells.

2. (Amended) The method of claim 1, wherein the [tumor] glioma cells are glioblastoma multiforme cells.

4. (Amended) The method of claim 1, wherein the glioma cells form a tumor in the mammalian subject and the growth of the tumor is inhibited.

5. (Amended) The method of claim [1] 4, wherein the tumor volume is reduced.

6. (Amended) The method of claim [1] 4, wherein the molecule is delivered by intratumoral injection.

14. (New) The method of claim 4, wherein the tumor is located in the cranium of the mammalian subject.

15. (New) The method of claim 14, wherein the IL13-moiety is hIL13.

16. (New) The method of claim 14, wherein the cytotoxic moiety is a Diphtheria toxin.

17. (New) The method of claim 14, wherein the cytotoxic moiety is a Pseudomonas toxin.

18. (New) A method of killing a glioma cell in situ, the method comprising the steps of:

(a) providing a mammalian subject having a cranium containing a glioma cell, the glioma cell comprising an IL13-specific receptor that specifically binds IL13 but not IL4;

(b) providing a molecule having an IL13-moiety and a cytotoxic moiety; and

(c) contacting the glioma cell with the molecule in an amount effective to kill the glioma cell.

19. (New) The method of claim 18, wherein the glioma cell is a glioblastoma multiforme cell.

20. (New) The method of claim 18, wherein the IL13-moiety is hIL13.

21. (New) The method of claim 18, wherein the cytotoxic moiety is a Diphtheria toxin.

22. (New) The method of claim 18, wherein the cytotoxic moiety is a Pseudomonas toxin.

APPENDIX B

1. (Amended) A method of reducing the rate of growth of glioma cells in vivo in a mammalian subject, the glioma cells comprising an IL13-specific receptor that specifically binds IL13 but not IL4, comprising the step of: delivering into the subject a molecule having an IL13-moiety and a cytotoxic moiety in an amount effective to reduce the rate of growth of the glioma cells.

2. (Amended) The method of claim 1, wherein the glioma cells are glioblastoma multiforme cells.

4. (Amended) The method of claim 1, wherein the glioma cells form a tumor in the mammalian subject and the growth of the tumor is inhibited.

5. (Amended) The method of claim 4, wherein the tumor volume is reduced.

6. (Amended) The method of claim 4, wherein the molecule is delivered by intratumoral injection.

14. (New) The method of claim 4, wherein the tumor is located in the cranium of the mammalian subject.

15. (New) The method of claim 14, wherein the IL13-moiety is hIL13.

16. (New) The method of claim 14, wherein the cytotoxic moiety is a Diphtheria toxin.

17. (New) The method of claim 14, wherein the cytotoxic moiety is a Pseudomonas toxin.

18. (New) A method of killing a glioma cell in situ, the method comprising the steps of:

(a) providing a mammalian subject having a cranium containing a glioma cell, the glioma cell comprising an IL13-specific receptor that specifically binds IL13 but not IL4;

(b) providing a molecule having an IL13-moiety and a cytotoxic moiety; and

(c) contacting the glioma cell with the molecule in an amount effective to kill the glioma cell.

19. (New) The method of claim 18, wherein the glioma cell is a glioblastoma multiforme cell.

20. (New) The method of claim 18, wherein the IL13-moiety is hIL13.

21. (New) The method of claim 18, wherein the cytotoxic moiety is a Diphtheria toxin.

22. (New) The method of claim 18, wherein the cytotoxic moiety is a Pseudomonas toxin.